Reliability of translaryngeal airway resistance measurements during maximal exercise

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Shareable abstract (@ERSpublications)
This is the first study to establish translaryngeal airway resistance as a reliable parameter in human respiratory medicine, allowing more informed treatment decisions and future research on the role of the larynx in health and disease https://bit.ly/3rnBRWS

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Abstract

Objective Exercise-induced laryngeal obstruction is an important cause of exertional dyspnoea. The diagnosis rests on visual judgement of relative changes of the laryngeal inlet during continuous laryngoscopy exercise (CLE) tests, but we lack objective measures that reflect functional consequences. We aimed to investigate repeatability and normal values of translaryngeal airway resistance measured at maximal intensity exercise.

Methods 31 healthy nonsmokers without exercise-related breathing problems were recruited. Participants performed two CLE tests with verified positioning of two pressure sensors, one at the tip of the epiglottis (supraglottic) and one by the fifth tracheal ring (subglottic). Airway pressure and flow data were continuously collected breath-by-breath and used to calculate translaryngeal resistance at peak exercise. Laryngeal obstruction was assessed according to a standardised CLE score system.

Results Data from 26 participants (16 females) with two successful tests and equal CLE scores on both test sessions were included in the translaryngeal resistance repeatability analyses. The coefficient of repeatability (CR) was 0.62 $\mathrm{cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}}$, corresponding to a CR% of 21%. Mean±SD translaryngeal airway resistance ($\mathrm{cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}}$) in participants with no laryngeal obstruction (n=15) was 2.88±0.50 in females and 2.18±0.50 in males. Higher CLE scores correlated with higher translaryngeal resistance in females (r=0.81, p<0.001).

Conclusions This study establishes translaryngeal airway resistance obtained during exercise as a reliable parameter in respiratory medicine, opening the door for more informed treatment decisions and future research on the role of the larynx in health and disease.

Introduction

Exercise-related breathing problems are common complaints in patients of all ages. Symptoms can be due to a range of different and often overlapping disorders, challenging our diagnostic skills in clinic and complicating phenotyping in research. Within respiratory causal pathways, workup is often targeted at conditions in the peripheral airways, particularly asthma and exercise-induced bronchoconstriction or its irreversible counterpart, COPD. However, the larynx is evidently heavily involved in exertional dyspnoea, both as the independent disease entity – exercise induced laryngeal obstruction (EILO) [1–4] – or as a contributing part of the bronchial obstruction in asthma [5, 6] and COPD [7]. These "upper *versus* peripheral airway interactions" are debated, exemplified by recent exchanges of opinions in the literature [8].

We have previously suggested that similar respiratory symptoms might be differentially interpreted by healthcare providers with different backgrounds, and that apparent disagreements might reflect a heterogeneous pathophysiology [9]. This situation is probably accentuated by the fact that most tools for evaluation of upper airway patency involve some degree of subjective assessment. EILO diagnostics relies on visual judgement of *relative* changes of the laryngeal inlet as these appear on endoscopic images during exercise [4, 10]. It is not given that the same degree of relative closure produces the same obstruction to ventilation nor the same sense of dyspnoea in different persons. This contrasts asthma and COPD, where diagnostic evaluations are supported by reproducible numerical data from spirometry. Thus, there is a need in respiratory medicine for numerical data that describe functional consequences of the relative laryngeal narrowing we can observe endoscopically or by using imaging techniques.

In veterinary medicine, airway pressure readings in equines have informed treatment decisions and research for years [11, 12]. Based on this experience, we have confirmed that translaryngeal airway pressure can be measured during high-intensity exercise also in humans [13]. As a first step to establish translaryngeal airway resistance as a valid parameter in respiratory medicine, reliability must be determined. Thus, the aims of this study were to investigate repeatability of translaryngeal resistance measured during maximal intensity treadmill exercise in healthy, non-smoking volunteers, and to use these data to indicate normative ranges for males and females.

Methods

Study design and participants

In this explorative study, participants were recruited from staff, students or associates of Haukeland University Hospital and Western Norway University of Applied Sciences, Bergen, Norway; all completing two tests within 2 weeks. All were healthy nonsmokers with no reports of exercise-related breathing problems, and symptoms of respiratory tract infections should not have been reported during the 2 weeks prior to tests.

The study was approved by the Regional Committee on Medical Research Ethics of the Western Norway Health Region Authority (2017/636/REK vest). Written informed consent was obtained from all participants.

Continuous laryngoscopy exercise test and the pressure recordings

Translaryngeal airway resistance was measured continuously during the continuous laryngoscopy exercise (CLE) test, which is a complete maximal cardiopulmonary exercise test (CPET) performed with a flexible laryngoscope positioned in the epi-pharyngeal area introduced *via* a transnasal route [10]. Translaryngeal resistance was calculated breath-by-breath based on airway pressure recordings obtained from two sensors placed above and below the larynx, and inspiratory airflow measured at the mouth [13].

Briefly, a 12-lead portable ECG was attached. The nostrils and nasal cavity were anaesthetised with lidocaine 4%. An endoscopic video camera system (Olympus Visera, CLV-S40; Olympus, Tokyo, Japan) was connected to a fiberoptic laryngoscope with work channel and diameter of 4.9 mm (Olympus ENF-VT3). The laryngoscope was advanced through a hole in a modified face mask (Hans Rudolph, Inc., Kansas City, MO, USA) through the nasal cavity to the oropharynx (figure 1). Lidocaine 4% was used to anaesthetise the vocal folds and proximal trachea, administered *via* an Olympus Spray tip catheter PW-6C-1 producing a mist. One milliliter was sprayed as the participant expressed a long “e” (closed vocal folds) and 1 mL with the vocal folds abducted. Further doses were given as required. Two pressure sensors (Mikro-Cath 825-0101, Millar, Houston, TX, USA) were introduced through the work channel, the first positioned approximately at the fifth tracheal ring and the second at the tip of the epiglottis (figure 1 and supplementary file 1 video). The laryngoscope was fixed to a custom-made headset. The sensors were secured to the headset and connected to a data acquisition box (Powerbox 8/35; ADIInstruments, Oxford, UK), with the data collected and stored on a MacBook Pro, Apple laptop using LabChart 8.0 software. Data acquisition was set at 40 Hz. Participants ran on a treadmill (Woodway PPS 55 Med; Woodway GmbH, Weil am Rhein, Germany) to individual experience of exhaustion using a modified Bruce protocol with 60-s incremental intensity steps. CPET variables (minute ventilation (V'_E), heart rate, peak oxygen consumption (V_{O_2}peak)) were recorded using a Vyntus SentrySuite Cardiopulmonary Exercise (CPX) unit powered by SentrySuite software (Vyaire Medical GmbH, Leibnizstrasse, Hoechberg, Germany).

Collection of pressure data and calculation of translaryngeal airway resistance

Pressures were continuously measured throughout the CPET. All reported variables and those used to calculate resistance were recorded close to peak exercise. Translaryngeal airway resistance was calculated breath-by-breath, based on corresponding pressure and flow values, using the following equation and given

FIGURE 1 Image of test situation.

as the mean of 10 consecutive breaths. Translaryngeal airway resistance was calculated by the following equation:

$$R_L = (P_T - P_E)/\mathrm{AF}$$

where

R_L is laryngeal airway resistance ($\mathrm{cmH_2O \cdot L^{-1} \cdot s^{-1}}$)

P_T is tracheal pressure reading ($\mathrm{cmH_2O}$)

P_E is epiglottic pressure reading ($\mathrm{cmH_2O}$)

AF is inspiratory airflow in litres/second ($\mathrm{L^{-1} \cdot s^{-1}}$) as determined by breath-by-breath data from the CPX unit.

Endoscopic evaluation

Three experienced clinicians viewed the endoscopic video feeds. CLE scores were noted at the end of test as described by MAAT *et al.* [14]. Briefly, supraglottic and glottic levels were scored separately, grade 0 being no obstruction, grade 1 mild obstruction, grade 2 moderate obstruction and grade 3 severe obstruction. For the purpose of this study, the expression 0/1 denotes obstruction grade 0 glottic and grade 1 supraglottic at peak exercise, and these were the maximum scores allowed in order to be defined as “no laryngeal obstruction” [15].

Statistics

Data were reported as mean±SD and differences with 95% confidence intervals. The coefficient of repeatability (CR) for translaryngeal resistance defines the value below which the absolute difference between two replicate measurements is expected to be found with 95% probability [16, 17]. Briefly, the CR is calculated as follows: The variance of the two observations from each subject is calculated by determining the difference between the two measures, squaring the value, and dividing by two. The square root of this value gives the within subject standard deviation (S_w). The CR can then be calculated: $CR=2.77\times S_w$ and accounts for both random and systematic errors. Both CR and CR % (CR as a percentage of the pairwise mean) were reported. CR is directly related to 95% limits of agreement (LoA) [16]. A plot of the SDs of the mean differences between repeated tests were made to visualise the relationship between the repeated tests, where the 95% LoA between the two tests were expressed as ±1.96 SD of the differences [18]. One-sample t-test *versus* zero was used to examine for systematic bias between the two tests. The differences between tests were regressed on the average to test for proportional bias, *i.e.*, whether the differences were influenced by the numerical magnitude of the measurement [19].

A preliminary normal range for translaryngeal resistance was calculated based on data from participants with normal laryngeal findings (here defined by CLE scores 0/0–1) reported as the mean value with SD and 95% confidence interval. Stratified by sex, the Kendall's Tau-b correlations coefficient (r) was used to measure the correlation between the translaryngeal resistances across the CLE categories.

The criterion for statistical significance was set at $p<0.05$. Statistical calculations were performed using the statistical software SPSS version 25 (IBM SPPS Statistics, Armonk, NY, USA) and MedCalc version 19.5.3 (MedCalc Software Ltd, Osted, Belgium).

Results

Participants

Altogether, 31 participants were recruited; their characteristics are given in table 1. All participants had a structurally normal larynx at rest. The overall distribution of CLE scores in the complete group of participants is depicted in figure 2. For repeatability calculations, we used the translaryngeal resistance data from 26 participants (16 females) with two successful tests and equal CLE scores on both occasions (table 2). Five subjects were excluded from the repeatability analyses, due to either attending only one test (n=4) or different CLE scores on two tests (n=1). To indicate normal values, we used the resistance data from the 15 subjects (6 females) with CLE scores rated as 0/0–1 (table 3).

Repeatability

There was no difference in translaryngeal resistance, maximal heart rate, peak oxygen consumption (V_{O_2}peak) and minute ventilation (V'_E) measured on the two repeated tests (table 2). For translaryngeal resistance, the CR was 0.62 $cmH_2O\cdot L^{-1}\cdot s^{-1}$, corresponding to a CR% of 21%. No constant or proportional bias was found for repeated measurements of translaryngeal resistance, visualised in the difference plot (figure 3).

Translaryngeal airway resistance

Mean±SD translaryngeal resistance ($cmH_2O\cdot L^{-1}\cdot s^{-1}$) in participants with CLE score 0/0–1 was 2.88±0.50 for females and 2.18±0.50 for males, with a mean (95% CI) difference between females and males of 0.71 (0.13–1.28) $cmH_2O\cdot L^{-1}\cdot s^{-1}$ (p=0.02) (table 3). Higher CLE scores were associated with higher translaryngeal resistance in females (r=0.81, p<0.001). The same did not apply in the male participants, however, acknowledging that only four males had higher CLE scores than 0/0–1 (figure 2).

TABLE 1 Characteristics of the 31 participants

	Females	Males
Subjects n	18	13
Age years	32.4±7.4	39.2±11.5
Weight kg	64.6±7.6	85.2±7.5
Height cm	166.9±6.4	183.5±5.3
BMI $kg\cdot m^{-2}$	23.2±2.5	25.3±2.0
Heart rate max $beats\cdot min^{-1}$	182±7	180±11
Peak minute ventilation $L\cdot min^{-1}$	106±14	153±22
Peak V_{O_2} $mL\cdot kg^{-1}\cdot min^{-1}$	44.2±6.4	45.7±8.0

Data presented as mean±SD unless otherwise stated. BMI: body mass index; V_{O_2}: oxygen consumption.

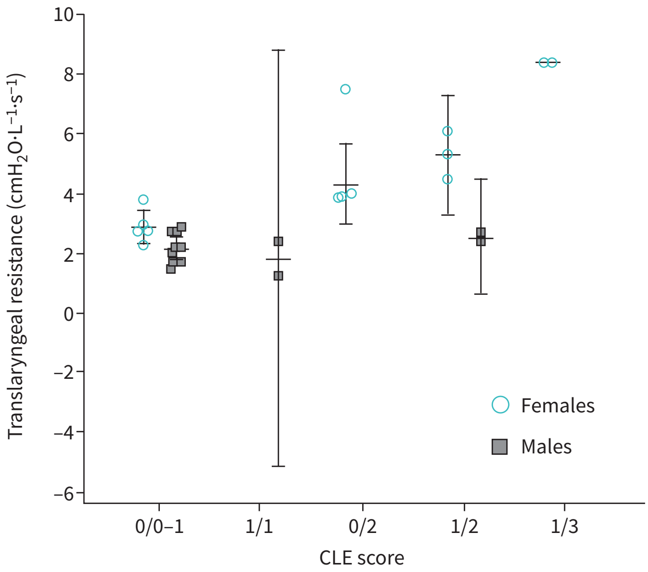

FIGURE 2 Error bars for the mean translaryngeal resistance with 95% confidence interval according to the continuous laryngeal exercise (CLE) score and sex. The first and the second digit in the CLE score category corresponds to the glottic and supraglottic score at maximal exercise, respectively.

Discussion

This is the first study to report translaryngeal airway resistance measured repeatedly in humans during high-intensity exercise. The repeatability was excellent and independent of the magnitude of laryngeal obstruction as defined by CLE scores. Translaryngeal resistance was higher in females than males. In females, there was a positive association between translaryngeal resistance and laryngeal obstruction as graded by CLE score, a finding we could not reproduce in males.

Laryngeal structure versus *function*

The larynx represents the single most important point of resistance of the airway tree, accounting for ~25% of total airway resistance during resting mouth breathing [20, 21]. The effort to overcome this resistance requires 12–30% of the total respiratory work, increasing with higher airflow and turbulence [21]. Most human bodily proportions exhibit some form of population distribution, and it seems reasonable to assume that this is also the case for laryngeal dimensions relative to body size and sex. The significance of this variation in health and disease is surprisingly poorly understood, given the critical role the larynx plays in the airways.

Resistance in a tube is proportional to the fourth power of the radius, and even minor laryngeal idiosyncrasies may have functional consequences that are clinically relevant. Thus, it is not surprising that laryngeal dimensions have been implicated in most major airway disorders. Already in 1991, Hurbis and Schild [22] indicated that the normal laryngeal response to exercise was distorted in asthma. Their findings

TABLE 2 Comparison of translaryngeal resistance and ergospirometry data obtained during two repeated treadmill exercise tests for the 26 participants attending the repeatability study

Measurements	Difference[#]	
	Mean	95% CI
Translaryngeal resistance $cmH_2O \cdot L^{-1} \cdot s^{-1}$	0.07	−0.06–0.20
Heart rate max $beats \cdot min^{-1}$	−0.1	−1.4–1.1
Peak minute ventilation $L \cdot min^{-1}$	−1.9	−5.1–1.3
Peak V_{O_2} $mL \cdot kg^{-1} \cdot min^{-1}$	−0.3	−1.3–0.7

V_{O_2}: oxygen consumption. #: paired difference.

TABLE 3 Translaryngeal resistance at peak exercise in participants with CLE score 0/0–1[#]

	Translaryngeal resistance $cmH_2O \cdot L^{-1} \cdot s^{-1}$	
	Mean±SD	95% CI
Females (n=6)	2.88±0.50	2.35–3.41
Males (n=9)	2.18±0.50	1.79–2.56

CLE: continuous laryngoscopy during exercise. [#]: the translaryngeal resistance is reported only for participants with CLE score 0/0–1 representing no glottic obstruction and no or mild supraglottic obstruction (0–1) at peak exercise.

have later been supported by studies applying imaging technology in patients with asthma and COPD [5–7, 23, 24]. Additionally, we have recently shown that noninvasive positive pressures applied to assisted cough in patients with respiratory insufficiency, inadvertently might infringe on laryngeal patency, leading to an unfortunate loss of therapeutic effect [25]. These studies all rest on rather crude imaging methods that address laryngeal structure and relative changes of size scored visually [6, 10]. We lack methods to produce numerical *absolute* data that reflect the functional consequences of these visual observations. More refined methods are required to move this field of respiratory medicine forward, and to ensure that clinical decisions and estimates of treatment effects are based on valid variables.

Repeatability of translaryngeal airway resistance

We have previously shown that translaryngeal pressures can be measured during high-intensity exercise [13]. This present study confirms the reliability of this technology, indicating that translaryngeal resistance can

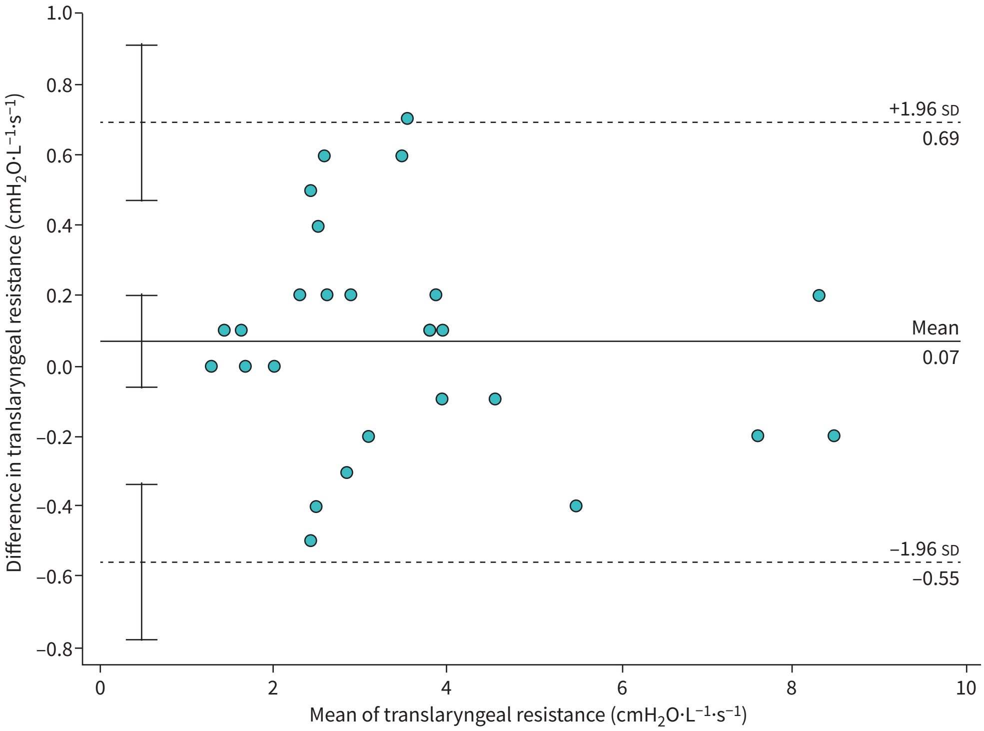

FIGURE 3 Agreement between translaryngeal resistance obtained from 26 subjects examined twice at peak exercise during a maximal exercise test on treadmill. The horizontal lines depict the mean difference between the translaryngeal resistance obtained in test 1 and test 2, whereas ±1.96 standard deviations of this difference represent the 95% limits of agreement between the two tests. The 95% confidence intervals for the mean, the upper limit of agreement and the lower limit of agreement are indicated by vertical lines. The mean difference was 0.07 $cmH_2O \cdot L^{-1} \cdot s^{-1}$, the upper limit of agreement was 0.69 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ and the lower limit of agreement was −0.55 $cmH_2O \cdot L^{-1} \cdot s^{-1}$.

be measured with a repeatability not very different from other parameters widely used in respiratory medicine, like spirometry [26].

When questioned before enrolment, all our participants refuted respiratory symptoms during exercise. Nevertheless, a surprisingly high proportion of females had CLE scores at peak exercise which were classified as more than "no obstruction". Their CLE scores were remarkably stable, and their data were therefore included in the repeatability calculations. We found that repeatability was not influenced by increasing CLE scores, nor by the magnitude of the translaryngeal resistance. We believe this increases the relevance of this study, indicating that translaryngeal resistance is a repeatable and valid parameter also in individuals with various degrees of laryngeal obstruction. There was no bias that suggested learning effects from repeated CLE tests; the mean difference between two replicate tests did not differ from zero.

Translaryngeal airway resistance versus *sex and relative laryngeal obstruction*

Most studies on vocal cord dysfunction and EILO suggest a female predominance, at least after puberty. Anatomical studies suggest similar laryngeal structure in boys and girls before puberty, while a male advantage regarding size seems to develop during puberty [27, 28]. This fits the prevalence data from two studies of EILO, with no sex difference in the study with 13- to 15-year-old participants, but a female predominance in the study with 14- to 24 -year-old participants [2, 29]. When addressing ranges for translaryngeal resistance in our study, we based the calculations on participants with no signs of obstruction during the test (CLE scores 0/0–1). The broad resistance ranges in our small population may partly reflect the low number of participants. However, these broad ranges are also consistent with the wide range of possible breathing patterns adopted at peak exercise, observed also with other respiratory parameters [30]. Translaryngeal resistance was 32% higher in females than in males in our adult population. This potential sex effect must clearly be tested in larger studies.

The number of participants with CLE scores exceeding 0/0–1 was too low to properly address relationships with the resistance measurements, and also not the aim of this study, as only subjects without exercise-related respiratory symptoms were enrolled. Nevertheless, in females with CLE scores exceeding 0/0–1, translaryngeal resistance was clearly outside the proposed "normal range" and also increasing with increasing CLE scores. On further questioning following the CLE test, inspiratory noise typical in EILO was reported by most of these subjects, but they had never considered this abnormal. This finding is supported by NORLANDER *et al*. [31], who conclude there is a need for more research and clearer criteria for claiming pathology in this area of respiratory medicine. Given these unexpected circumstances, data from these females who had not considered their laryngeal obstruction a respiratory problem cannot be used to indicate which level of laryngeal resistance is likely to be found in typical EILO patients. These findings will therefore need to be confirmed in the target population, patients presenting with symptoms of EILO. However, we propose that these findings represent an incipient functional validation of the observed structural laryngeal changes in EILO [14].

Translaryngeal resistance tended to be lower in males, independent of their CLE scores, also in the few males with CLE scores exceeding one. Regrettably, too few observations prevent statistical handling of this sex aspect. Nevertheless, one may speculate whether males have a larger "laryngeal reserve capacity" for airflow, allowing some degree of inward displacement of laryngeal structures without leading to higher airflow resistance. These speculations support the notion that EILO symptoms are more common in females than males.

Strengths, limitations and weaknesses of the study

This study opens a novel research area in human respiratory medicine; real-time functional assessment of the larynx during high-volume ventilation. The strengths of the study were a staff with decades of experience in EILO research and clinical work, a well-equipped exercise laboratory, and interdisciplinary collaboration between specialists from a wide range of disciplines.

The main limitation was the overall low number of participants, which prevents firm conclusions, particularly as regards normal ranges and sex differences. Also, our adult population above 24 years of age does not reflect the typical EILO patient, who most frequently present as a teenager [9]. Explorative research in healthy subjects under the age of 16 years presents greater ethical issues, particularly when testing a method that may be judged slightly unpleasant, and we therefore started with an adult population. However, we clearly need studies with broader participant demographics to establish normal values.

Introducing a pressure transducer below the vocal folds requires the use of topical lidocaine, which may alter the laryngeal response to exercise. It is currently not established how and to what extent local anaesthetics affect upper airway mechanics; but it has been suggested that laryngeal hyposensitivity is associated with an increased risk of EILO [32]. Our finding that participants with no recollection of respiratory symptoms during exercise in fact did develop laryngeal obstruction during testing may support this theory. We need a better understanding of potential effects of lidocaine on upper airway functions to fully exploit this method in clinical work and research.

Future perspectives

Airway pressure measurements have informed clinical work and treatment decisions in equine upper respiratory tract surgery for years [11, 12]. We acknowledge that widespread use of this method in humans currently is limited by lack of commercially available equipment that can ensure smooth implementation in routine work. We also need to establish some very basic information, *e.g.* normal ranges relative to body size, ventilation volume and sex. The applicability of this technology during the extreme scenario of high-intensity exercise suggests its feasibility also in patients at rest. We predict that translaryngeal resistance might become integrated in future advanced diagnostic evaluations in respiratory medicine, and perhaps also guide our ambition to optimise treatment tools that rest on noninvasive application of positive pressures, a current treatment challenge.

Conclusion

We conclude that translaryngeal airway resistance can be measured at peak exercise in "average people", and that the technology appears robust in terms of applicability and repeatability. We found that females had higher resistance than males, and that higher degrees of laryngeal obstruction in females were associated with higher resistance, a finding that needs to be confirmed in patients with symptomatic EILO. The study opens a novel research area in human respiratory medicine, *i.e.* real-time functional assessment of structural laryngeal response patterns, as these can be observed by endoscopy or imaging techniques.

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